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Formulation and Evaluation of Teneligliptin and Telmisartan Bilayer Tablets for the Treatment of Coexistent Type II Diabetes Mellitus and Hypertension

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ABSTRACT

In the current scenario type two diabetes mellitus and hypertension have become prevalent in large number of population. But there are many patients which are suffering from Type II Diabetes Mellitus as well as hypertension. Such condition is called co-existent Type II Diabetes Mellitus and Hypertension. In the present work an attempt is made to treat co-existent type II Diabetes Mellitus and hypertension by formulating a Bilayer tablet of Teneligliptin and Telmisartan. Both drugs are sustained released to give a day long relief to the patients and to also reduce the dose frequency. Both the layers of the tablets were formulated by wet granulation method. The granules were tested for angle of repose, bulk density, tapped density, compressibility and Hausner's ratio to check their efficacy. Eleven different types of formulations were made using various polymers and excipients with the drugs such as PVP K30, HPMC K4M, Starch, Crospovidone, Lactose, Mannitol, Talc and Magnesium Stearate. From these 11 formulations F6 showed better tablet characteristics and drug release rate than other formulations. Thus F6 is the best formulation in this study. Biological screening of the drugs combination of Teneligliptin and Telmisartan was also done to check the presence of antidiabetic activity of the combination which showed positive results.

Keywords: - Teneligliptin, Telmisartan, Sustained, Bilayer.

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INTRODUCTION:

In this modern world of faster and hectic lives, eating healthy and staying fit is ignored. Such ignorance may lead to various harmful diseases and disorders. Diabetes mellitus is such kind of disorder which if not managed properly may prove fatal. Type II Diabetes mellitus is the most harmful type of diabetes as the body of the patient becomes insulin resistant. Also hypertension is present in large number of populations. But when these two severe diseases are present coexistently in an individual, additional care is needed to be taken. Coexistent Type Two Diabetes Mellitus (TTDM) and hypertension exposes patients to severe co-morbidities.

Hypertension (HTN) is present in more than 50% of patients with diabetes mellitus (DM) and contributes significantly to both micro and macrovascular disease in DM. Indeed, the risk for cardiovascular disease (CVD) is four-fold higher in patients with both DM and HTN as compared to the normotensive non-diabetic controls. To this point, a meta-analysis of 102 prospective studies involving 698,782 individuals found that DM is responsible for approximately a two-fold increased risk for coronary heart disease, stroke and deaths from cardiovascular cause, including heart failure, cardiac arrhythmia, hypertensive disease, etc. In developed countries 60-65% prevalence is seen in coexistent type II diabetes mellitus and hypertension. Complex polypharmacy suggested by international organizations leads to the increased pill burden and decreased patient compliance which leads to worsening of conditions[1,2].

Hence there is a need for a combination of antidiabetic and antihypertensive drugs for the treatment of coexistent type two diabetes mellitus and hypertension.

MATERIALS:-

Teneligliptin was provided as gift sample from Lupin Pharmaceuticals Limited, Pune whereas Telmisartan was obtained from Abbott Healthcare Pvt. Ltd. Himachal Pradesh as gift samples. Polymers and excipients such as HPMC K4M, PvpK30, crospovidone, talc etc were purchased from JP. Fine chemicals and Loba Chemise Pvt. Ltd.

METHODS:-

Various techniques can be used to formulate bilayer tablets. Wet granulation is one of the techniques used to formulate the two layers of tablets. Wet granules of both layers are formulated individually. Wet granulation techniques have various advantages. Hence it is a method of choice for many tablet formulations. It enhances the flow properties of powder mix. It avoids segregation of powder components during tabletting or storage. It also reduces cross-contamination and hazard associated with the generation of toxic dust that may arise during manufacturing process. Wet granulation not only improves the compression characteristics of drug substances as well as improves the appearance of the final product. Wet granulation involves use of water for granulation. Aqueous binder solution is added to the dough mass and then sieved to produce the required size of granules. Tablets made from wet granulation techniques have better hardness and appearance then directly compressed tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated. Moreover this technique improves the dissolution characteristics of the poorly water-soluble drugs by allowing uniform distribution of the binder that acts as a wetting agent and enable adequate wetting of the drug substance during granulation. It also increases the chances of adequate and uniform contact between the drug and hydrophilic polymer for better dissolution. These improved granule characteristics also results in even erosion of tablets during dissolution [4,15].

➢ **Preparation of Tablet by Wet Granulation :**

- **Wet Granulation of Sustained Release Telmisartan Layer :-**

Wet granulation is the most widely used to prepare tablets. Formulation with different binders was compressed into tablets. The required quantities of Telmisartan ,starch ,lactose monohydrate ,HPMC K4M, crospovidone were weighed accurately using analytical balance and were mixed well using laboratory conditions. The aqueous binder solution was added and mixed thoroughly to form dough mass. Carmiosine Colour was added to the aqueous binder solution for Telmisartan granules to provide visual detection of two different layers in the bilayer tablets. The formed mass was passed through Mesh no.12 to obtain wet granules .The wet Granules were dried in a hot air oven at 300 c temperatures. then the dried granules were passed through mesh no.16 to break aggregates. Talc & magnesium stearate were passed through mesh no.100 on to dry granules and blended in a polyethylene bag .The Tablet granules were then compressed using compression machine at punch No. 5 [11,15].

- **Wet Granulation of Sustained Release Teneligliptin Layer :-**

Wet granulation is done for this layer of Bilayer tablet too. This layer consists of drug/API. Teneligliptin(20mg) and various excipients which act as binders, diluents and lubricants in the formulation. These are starch, mannitol and magnesium stearate respectively. HPMC K4M is the sustained releasing agent. The aqueous binder solution was added and mixed thoroughly to form a dough mass. The formed dough mass was passed through Mesh no.12 to obtain wet granules of Teneligliptin layer. The wet granules were dried in a hot air oven at 300 ^{o}c temperatures. On drying, the dried granules were passed through mesh no.16 to break aggregates if formed. Talc & magnesium stearate were passed through mesh no.100 on to dry granules and blended in the polyethylene bag kept for these granules. The Tablet granules were then compressed using compression machine at punch No. 5 over the Telmisartan layer.

Thus, The Bilayer Tablet is formed by the Above Mentioned Processes

Compositions of Bilayer Tablets

Table No.1: Compositions of Sustained Release Layer of Teneligliptin :-

Sr. No.	Ingredient mg/Tablet	F1	F2	F3	F5	F4	F6	F7	F8	F9	F10	F11
1	Teneligliptin	20	20	20	20	20	20	20	20	20	20	20
2	HPMC K4M	105	105	105	105	53	105	105	105	105	105	105
3	PVP K30	20	-	-	-	-	-	-	-	-	-	-
4	Starch	55	55	55	82	55	82	82	55	55	55	55
5	Lactose	34	54	-	27	106	-	07	-	44	34	24
6	Mannitol	-	-	54	-	-	27	-	34	-	-	-
7	Crosspovidone	-	-	-	-	-	-	20	20	10	20	30
8	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3
9	Talcum	3	3	3	3	3	3	3	3	3	3	3
10	P. Water	Q.S.	Q.S.	QS	QS	Q.S	QS.	QS.	QS	Q.S	Q.S	Q.S
	Total Weight	240	240	240	240	240	240	240	240	240	240	240

Table No.2 : Compositions of Sustained Release Layer of Telmisartan :-

Sr. No.	Ingredient mg/Tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	Telmisartan	40	40	40	40	40	40	40	40	40	40	40
2	HPMC K4M	105	105	105	53	105	105	157	105	105	105	105
3	PVP K30	40	-	-	-	-	-	-	-	-	-	-
4	Starch	55	55	55	55	27	27	27	27	55	55	55
5	Lactose	14	54	-	106	82	62	10	-	44	34	24
6	Mannitol	-	-	54	-	-	-	-	62	-	-	-
7	Crosspovidone	-	-	-	-	-	20	20	20	10	20	30
8	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3
9	Talcum	3	3	3	3	3	3	3	3	3	3	3
10	P. Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
	Total Weight	260	260	260	260	260	260	260	260	260	260	260

Total Weight of Each Bilayer Tablet was Thus 500mg for All prepared Formulations.

- **Pre-Compression Characteristics [2,4,7,8]:**

The following parameters are determined.

1 Angle of Repose:

The angle of repose has been used to characterize the flow properties of solids. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

2 Bulk Density

The ratio of mass (weight) to volume is known as the bulk density of material. The bulk density is obtained by dividing the weight of the sample in grams by final volume in cm^3.

3 Tapped Density

Tapped density is determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus which is operated for fixed number of taps (~ 100) until a powder bed volume has reached the minimum.

4 Compressibility Index

The compressibility index of the powder was determined by Carr's index. The Carr's index is determined from the tapped density and poured density (bulk density) as per its formula.

5. Hausner's Ratio

Hausner's ratio is determined from the ratio of tapped density to bulk density using its standard formula.

- **Evaluation of Post Compression Parameter:**

1) General Appearance:

General appearance would include a number of aspects like size, shape, odor, taste, texture, legibility and identifying marks.

2) Size and Shape:

Different shapes and size of tablet are available in the market they are manufactured in order. The shape and size of a tablet would vary based on tooling used in the tablet manufacturing. In laboratory scale tablet size measured by the Vanier caliper. Tablet thickness should be controlled within ±5% variation of a standard value.

3) Hardness:

Tablet hardness and strength are the essential to see that the tablet can with the shock and stress during manufacturing packaging and transportation, and while handle by the patient. For each formulation, the hardness of tablet determined using the Monsanto hardness tester.

4) Friability:

Friability is the test for a tablet those whether the tablet is stable to abrasion or not, it is tested by using Roche Friabilitor.

5) Weight Variation:

Weight variation test is performed to check that the manufactured tablets have a uniform weight. For a tablet to pass the test not more than 2 tablets should lie out of the specified percentage and if no tablet differ by more than two times the percentage limit.

Table No. 3: Standard Limits for Weight Variation as per I.P.

Sr. No.	Average weight of Tablet (mg)	Maximum Percentage difference allowed
1	80	10
2	80-250	7.5
3	>250	5

Table No.4: Standard Limits for Weight Variation as per USP

Sr. No.	Average weight of Tablet (mg)	Maximum Percentage difference allowed
1	130/ Less	10
2	130-324	7.5
3	>324	5

6) Drug Content [2,15,16] :

From each batch 3 tablets were weighed each containing 10 mg of tablet were taken. Tablets were triturated in motor and quantity of powder equivalent to 10 mg of tablet powder was transferred to 100 ml volumetric flask. Sufficient quantity of Phosphate buffer solution PH 6.8 was added with shaking and volume was made up to the mark and filtered through whatman filter paper. Further dilutions were made in concentration 2, 4, 6, 8, 10ug/ml. then absorbance was recorded at different wavelength of drugs such as (Teneligliptin at 243.6 nm and Telmisartan at 295 nm) against phosphate buffer solution PH 6.8 as a blank.

7) In vitro Disintegration Time [6,14]:

In vitro disintegration time of the tablet was determined using USP disintegration test apparatus as per I.P. specifications. It is determined by using USP device which consisted of 6 glass tubes that are 3 inches long. Open at one end and held against 10 mesh screen at the bottom end of basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned in a 1 liter basket assembly up and down. To compliance with the USP standard, all tablet must disintegrate and all particles must pass through the 10 mesh in the time specified. [56, 58]

8) In vitro Dissolution Study [15,18]:

Dissolution profiles of bilayer tablets were determined using the USP method II with paddle speed at 50 rpm. The media used in dissolution apparatus was phosphate buffer PH 6.8 (900ml) and maintained it at 37 ± 1^0 C. the 2ml of sample were withdrawn at 0, 30, 60, 90, 120, 180, 240, 300, 360, 420 minutes time intervals.. 5ml diluted with 10ml of phosphate buffer solution, and analyzed at 243.6 nm and 295nm using UV-Visible double beam spectrophotometer (JASCO V-630).

Table No.5 : Procedure for Dissolution Study

Parameters	Conditions
Dissolution media	900ml of phosphate buffer solution PH 6.8
Temperature	37±1^0 C
RPM	50
Drug Content	Weigh of tablet equivalent to 500 mg
Volume Withdrawn	2ml
Volume made up to	10ml
Λmax	243.6nm and 295nm.
Dilution Factor	5

9) Stability Study:

ICH recommends carrying out stress testing on the drug substance to establish its inherent characteristics and support the solubility of the proposed analytical procedure. Stability study at room temperature is the method of determining the actual shelf life of the product. Unfortunately it is difficult to make an accurate expiration date prediction until 2-3 yrs. Of data are generated, which will require long shelf life conditions. Hence accelerated stability studied were carried out at elevated temperature will help to determine shelf life within a lesser period of time. The prepared tablets were evaluated for a period of one to three month as per ICH Guidelines. [58]

➢ Biological Screening:

A] Antidiabetic Activity-

Experimental Procedure: The compounds extracted during the present work were subjected to alloxan induced antidiabetic activity.

Requirements-

Standard drug: - Metformin Hydrochloride (120mg/kg p.o. body weight in 0.25% CMC solution)

Test Combinations [19,20,23] :-

The Test combinations are taken as :

1) Teneligliptin :- 0.01 mg/kg p.o + Telmisartan 1mg/kg p.o. in 0.25% MC solution,

2) Teneligliptin :- 0.1 mg/kg p.o + Telmisartan 1mg/kg p.o. in 0.25% MC solution,

3) Teneligliptin :- 1 mg/kg p.o + Telmisartan 1mg/kg p.o. in 0.25% MC solution

Chemicals:-Alloxan monohydrate(150mg/kg i.p.)

Apparatus: - Glucometer, Disposable syringe (1ml tuberculin syringe), feeding needles (for oral dose), Polypropylene cage.

Procedure-

Wistar rats either sex weighing between 150-200gm were used. The animals were housed under controlled conditions with standard diet and water. The animals were kept fasted for 24hrs with water , diabetes was induced by Alloxan monohydrate (120mg/kg i.p) in normal saline solution.

A 5% dextrose solution was given in feeding bottle for a day to overcome early hypoglycemic phase. The blood glucose level was monitored by taking blood tail tip cut method on glucometer.

After 72 hrs,the animals showing blood glucose level beyond 150mg/dl were segregated and were divided into 3 groups.viz...(i) vehicle treated group (ii) standard treated group, (iii) drug treated group comprised 5 subgroups for 3 test combinations. Each group as well as subgroup comprised of 6 animals.The doses of combination of Teneligliptin and Telmisartan to be administered to wistar rats based on the available references of individual drugs was calculated. (for acute study).

B] Blood Sample Collection From Tail Vein:-

1) Prevent the animal by using the mechanical restraint device with the tail of the animal protruding. Use antiseptic solution to clean the area; do not rub back and forth to prevent

degradation of quality of sample. Prevent the tail from moving with non-dominant hand and rotate ¼ turn to work on the lateral tail vein. 2) Align the needle parallel to the tail with the sloping edge of the needle to be used facing up. Insert needle into the tail vein starting at the tip of the tail (distally) i. Gently aspirate it to collect by syringe; ii. Observe blood flash by syringe insertion and let the blood drip from needle hub into collection tube or into hematocrit tube by capillary action; iii. Remove the inserted needle from the vein and collect blood droplets in the collection tube or into hematocrit tube by capillary action. 3) Put gentle pressure with the help of gauze for just 15 to 30 seconds until

bleeding from the vein has stopped. If the blood does not stops, clotting agent can be used to stop the blood flow. 4) Throw or dispose the needle well. If the animal is administered with an anesthetia, monitor the animal till it is fully awake and it is able to move normally. Repetitive bleeds for blood collection may be performed by insertion of the needle further up the tail.

C] Methodology:-Collection of Blood:-

Table no. 6 Biological activity profile table (A1, B1, C1 are doses of Teneligliptin and A2, B2, C2 are doses of Telmisartan respectively.

Sr.No.	Groups (N=6)	Treatment and dose day	Observation
1	Group-I	Vehicle control(1ml saline water p.o.) 0 to 28 day.	1) Estimation of blood glucose level on 2nd,4th,6th, 8th,10th and 28th days. 2) Stastistical analysis by ANOVA followed by Dunnett's test.
2	Group-II	Negative control Alloxan monohydrate(150mg/kg i.p.) for 0 to 2 days	
3	Group-III	Positive control Alloxan Monohydrate(150mg/kg) for 2 days + Metformin hydrochloride(50mg/kg) p.o. for next 26 days.	
4	Group-IV	Alloxan monohydrate(150mg/kg) i.p.+ test drugs A1(0.1mg/kg) + A2(1mg/kg) p.o.	
5	Group-V	Alloxan monohydrate(150mg/kg) i.p+ test drugs B1(1mg/kg) + B2(1mg/kg) p.o	
6	Group-VI	Alloxan monohydrate (150mg/kg) i.p+ test drugs C1(10mg/kg) + C2(1mg/kg) p.o.	

RESULTS AND DISCUSSION:

IR Spectroscopy Analysis:

- The IR Spectrum of the drug agrees with its chemical structure 6-chloro-4hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2, 3

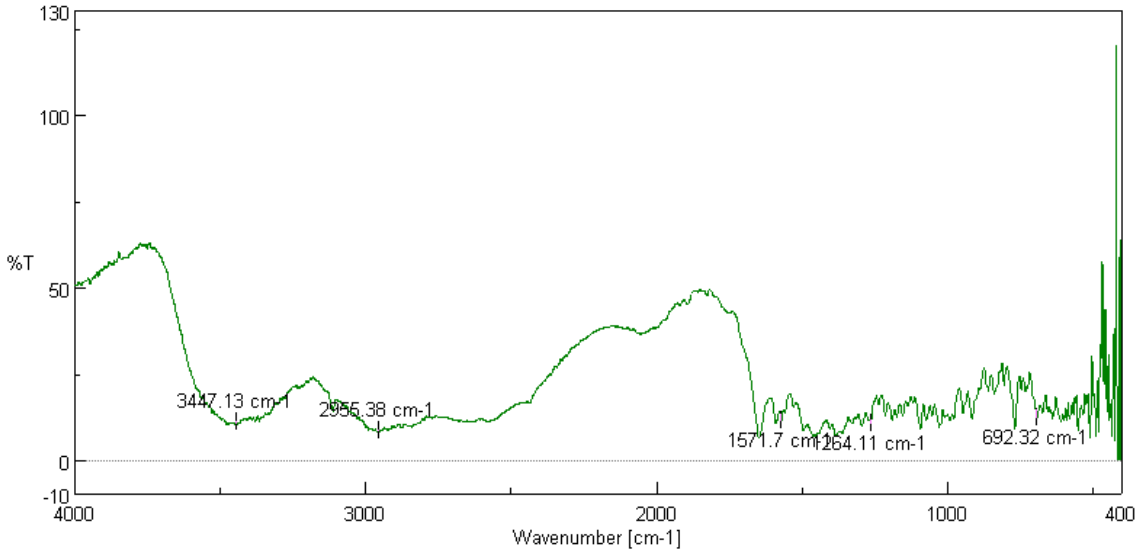

Figure No. 1: Infrared Spectrum of Teneligliptin

Table No. 7: IR Peak Value of Teneligliptin

Sr. No.	Absorption Peak cm^{-1}	Attributed to Functional Group	Type of Vibrations
	3447.13	N-H	Stretching
	2956.87	C-H	Stretching
	1571.7	C-C	Stretching
	692.32	C-S	Stretching

The IR Spectrum of the drug agree with the chemical structure (RS)-2-(3-benzoylphenyl)-propionic acid.

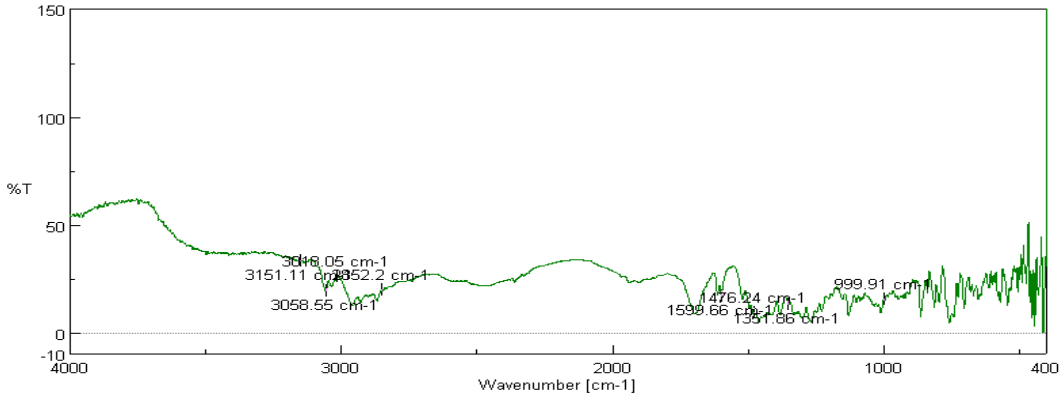

Figure No.2: Infrared Spectrum of Telmisartan

Table No. 8: IR Peak Value of Telmisartan

Sr. No.	Absorption Peak cm^{-1}	Attributed to Functional Group	Type of Vibrations
	3151.11	C-H	Stretching
	1476.24	C=C	Stretching
	999.91	C-N	Stretching

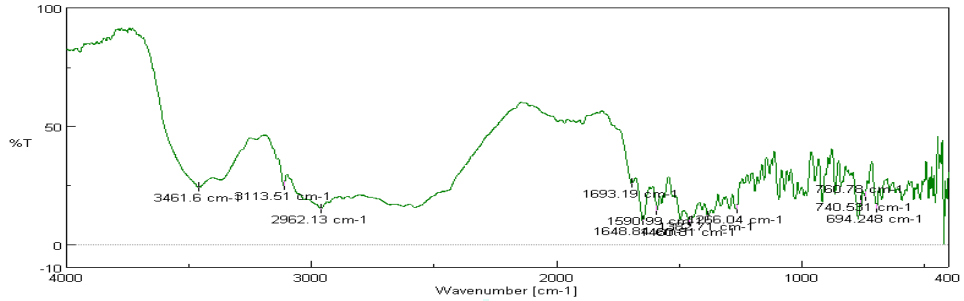

Figure No. 3: IR Spectrum of Teneligliptin and Telmisartan Mixture with Polymers

Table No. 9: IR Value of Teneligliptin and Telmisartan Mixture with Polymers

Types of Bonds	Wave Number /cm^{-1} Found
N-H Stretching	3456.78
C-H Stretching (Methyl)	2970.8
C-H Stretching Vibration of (aromatic ring)	3114.47
C=O Stretching Vibration of Amide Moiety	1650.77
Aliphatic C-H Stretch	2962.13
CH2 (Bending)	1461.78
C=C Stretching/bending	1599.66
COOH bending	1381.75
COOH Acid	1696.09
Disubstituted benzene	741.496 758.852
C-N Stretching	1265.07
C-S	694.248

The peaks observed in pure samples of Teneligliptin and Telmisartan drugs sample determined by IR analysis are one and same as the reference graph. The peaks observed in the IR graph of the mixture sample of Teneligliptin and telmisartan with the polymers which are used in the formulation are in same position / state as that of the IR Spectrum of pure sample.

Thus justified that there is no or minimal interaction of binders with the drug molecules. Hence there is no obstacle in using these binders to formulate the tablet.

5. Differential Scanning Calorimetry:

The DSC thermogram of Teneligliptin showed a sharp exothermic peak at 210.6^{0}C. Telmisartan exhibited single,

sharp endothermic peak at 275.6^{0}C. The obtained values are much close to reported value of Teneligliptin and Telmisartan Melting Point. The Teneligliptin and telmisartan bilayer Tablet Formulation exhibited double, sharp endothermic peaks at 355.43^{0}C, 260.73^{0}C and 170.91^{0}C.

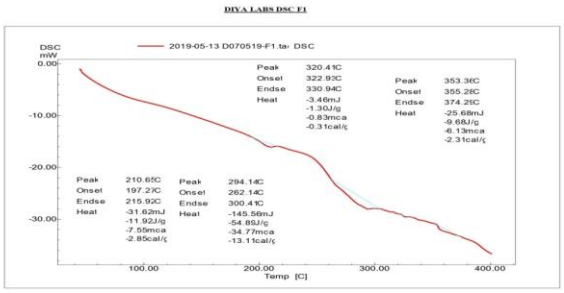

Figure No. 4: DSC Graph of Teneligliptin

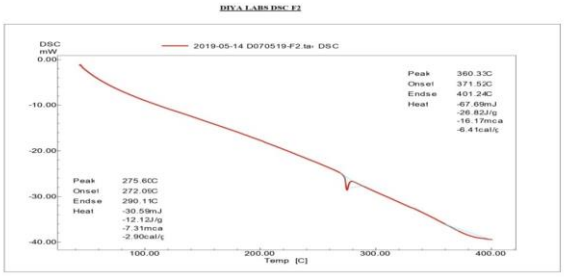

Figure No. 5: DSC Graph of Telmisartan

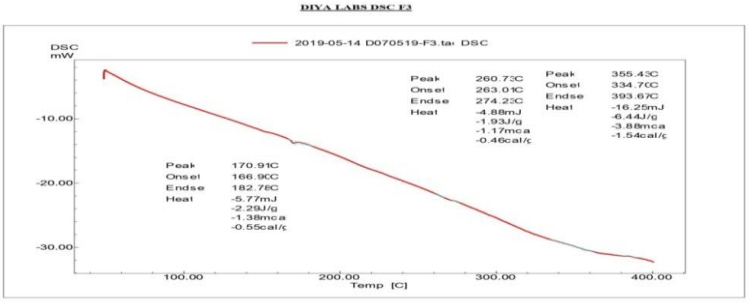

Figure No. 6: DSC Graph of Teneligliptin and Telmisartan Bilayer Tablet Formulation

6. Calibration Curve of Teneligiptin:

The standard calibration curve shows the slope of 0.065 and correlation coefficient of 0.998. The curve was found to be linear in the concentration range of 2, 4, 6, 8, 10µg/ml at 243.6 nm. The calculation of drug content, in vivo dissolution study was based on the calibration curve.

Table No. 10: Calibration Curve of Teneligliptin

Sr. No.	Concentration (µg/ml)	Absorbance at 243.6 nm
	0	0
	10	0.1991
	20	0.3871
	30	0.5928
	40	0.7876
	50	0.9578

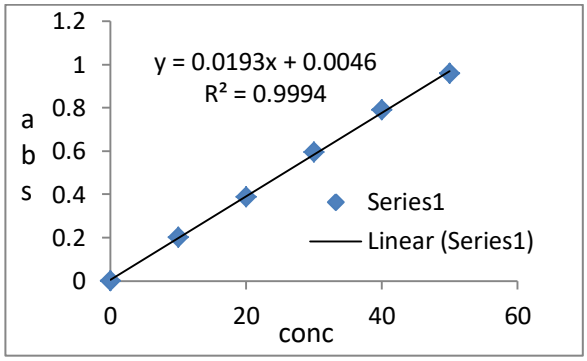

Figure No. 7: Calibration Curve of Teneligliptin

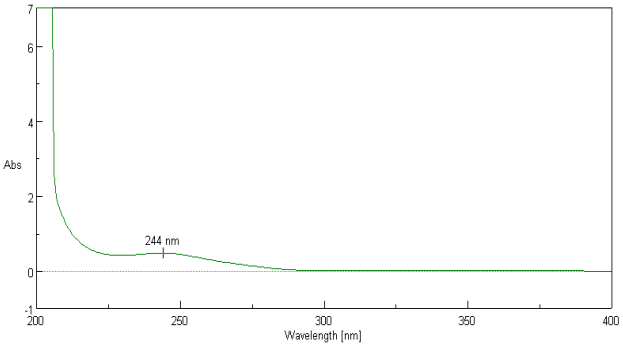

Figure No. 8: UV Spectrum of Teneligliptin

Tablet No. 11: UV Parameter for calibration curve in pH 6.8 buffer solution

Sr. No.	Parameters	Value in pH 6.8 phosphate buffer solution
1	Absorbance maximum (λmax) in nm	243.6nm
2	Slope	0.0193
3	Intercept	0.0046
4	Correlation Coefficient	0.9994
5	Equation	Y= 0.0193X + 0.0046

7. Calibration Curve of Telmisartan:

The standard calibration curve of Telmisartan was obtained by plotting Absorbance vs. Concentration. Table No. 12 shown the absorbance values of Telmisartan. The standard curve is shown in Figure 9.9. The standard calibration curve shows the slope of 0.075 and correlation coefficient of 0.996. The curve was found to be linear in the concentration range of 2, 4, 6, 8, 10µg/ml at 295 nm. The calculation of drug content, in vivo dissolution study was based on the calibration curve.

Table No. 12: Calibration Curve of Telmisartan

Sr. No.	Concentration (µg/ml)	Absorbance at 295 nm
	0	0
	2	0.136
	4	0.2553
	6	0.3794
	8	0.5151
	10	0.6471

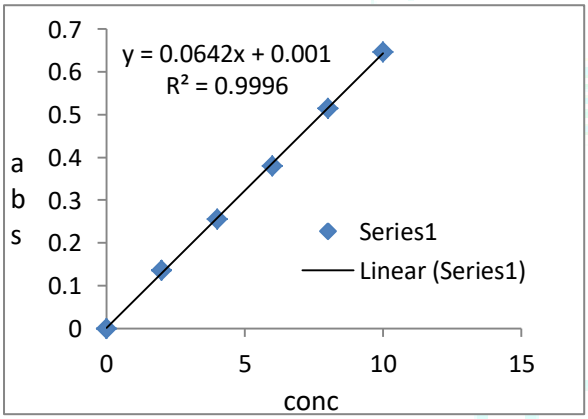

Figure No. 9: Calibration Curve of Telmisartan

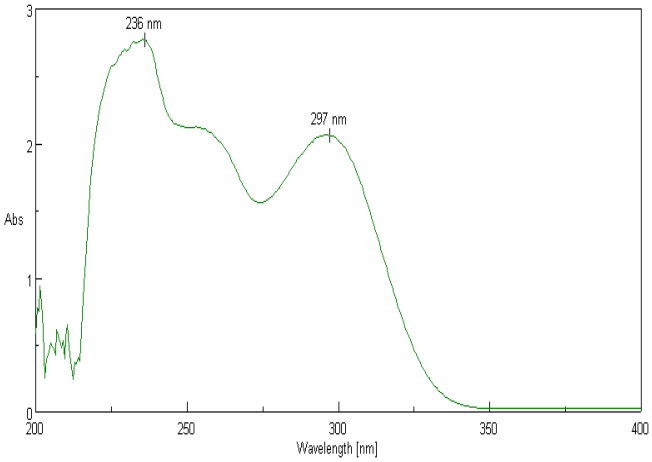

Figure No. 10: UV Spectrum of Telmisartan

Tablet No. 13: UV Parameter for calibration curve in pH 6.8 buffer solution

Sr.No.	Parameters	Value in pH 6.8 phosphate buffer solution
1	Absorbance maximum (λmax) in nm	295nm
2	Slope	0.0642
3	Intercept	0.001
4	Correlation Coefficient	0.9996
5	Equation	Y= 0.0642X+ 0.001

Characterization of Granules of API and Excipients:

For each type of preliminary formulation blends, blends of API and Excipients were prepared and evaluated for various parameters as explained earlier.

Table No.14: Characterization of Telmisartan Granules :-

Formulation Batches	Evaluation Parameters				
	Angle of Repose	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Compressibility Index (%)	Hausner Ratio
F1	27.49⁰	0.67	0.75	10.66	1.11
F2	24.73⁰	0.72	0.79	8.86	1.09
F3	25.33⁰	0.75	0.83	9.63	1.10
F4	25.69⁰	0.77	0.81	4.93	1.05
F5	27.35⁰	0.69	0.75	8.00	1.08
F6	25.37⁰	0.76	0.82	7.31	1.070
F7	26.23⁰	0.78	0.84	7.14	1.076
F8	24.82⁰	0.66	0.72	8.33	1.09
F9	26.47⁰	0.70	0.75	6.66	1.071
F10	25.84⁰	0.71	0.78	8.97	1.09
F11	26.77⁰	0.75	0.80	6.25	1.06

Table No.15:- Characterization of Teneligliptin Granules :-

Formulation Batches	Evaluation Parameters				
	Angle of Repose	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	Compressibility Index (%)	Hausner Ratio
F1	25.39⁰	0.63	0.68	7.35	1.07
F2	22.46⁰	0.65	0.71	8.45	1.09
F3	24.85⁰	0.71	0.75	5.33	1.05
F4	23.49⁰	0.72	0.77	6.4	1.06
F5	25.15⁰	0.68	0.70	2.85	1.02
F6	26.61⁰	0.75	0.79	5.06	1.05
F7	23.53⁰	0.66	0.73	9.58	1.10
F8	24.11⁰	0.64	0.69	7.24	1.07
F9	22.36⁰	0.69	0.75	8.00	1.08
F10	22.56⁰	0.71	0.76	6.57	1.07
F11	23.53⁰	0.70	0.77	9.09	1.10

- **Evaluation of Compressed Tablets:**

All the tablet formulation were subjected for Organoleptic, Physical and Chemical evaluation as shape. Thickness, Hardness, Friability, Weight Variation, In-vitro Disintegration Time, Drug Content, And In-vitro Dissolution Studies.

Table No.16: Evaluation of Formulated Batches

Sr. No.	Formulations	Thickness (mm ± SD)	Hardness (kg/cm²)	Friability (%)	Weight Variation (mg ± SD)
1	F1	3.49	4.23	0.57	497 ± 0.75
2	F2	3.30	4.45	0.45	494 ± 0.50
3	F3	3.25	4.67	0.61	498 ± 0.75
4	F4	3.29	4.98	0.71	496± 0.50
5	F5	3.75	5.19	0.41	491± 0.75
6	F6	3.43	4.71	0.67	499± 0.50
7	F7	3.37	4.55	0.83	501± 0.50
8	F8	3.63	5.10	0.57	495± 0.75
9	F9	3.26	4.81	0.91	503± 0.75
10	F10	3.88	4.38	0.48	492± 0.50
11	F11	3.54	4.73	0.84	498± 0.50

Table No.17: Evaluation of Post-Formulated Batches

Sr. No	Formulations	Diameter (mm ± SD)	Disintegration Time (min.)	% Drug Content		% Drug Release in (420 mins.)
1	F1	10±0.00	62 min	Teneligliptin	96.13	23.2
				Telmisartan	95.20	20.53
2	F2	10±0.00	71 min	Teneligliptin	97.48	19.03
				Telmisartan	95.63	14.70
3	F3	10±0.00	76 min	Teneligliptin	96.32	35.61
				Telmisartan	96.65	27.32
4	F4	10±0.00	87 mins	Teneligliptin	97.23	22.65
				Telmisartan	96.35	15.32
5	F5	10±0.00	69 mins	Teneligliptin	98.75	23.78
				Telmisartan	99.27	18.55
6	F6	10±0.00	110 mins	Teneligliptin	98.58	49.45
				Telmisartan	98.72	43.81
7	F7	10±0.00	79 mins	Teneligliptin	96.54	29.05
				Telmisartan	96.23	25.30
8	F8	10±0.00	115 mins	Teneligliptin	95.81	38.28
				Telmisartan	96.75	31.10
9	F9	10±0.00	92 mins	Teneligliptin	97.38	23.48
				Telmisartan	96.87	19.42
10	F10	10±0.00	107 mins	Teneligliptin	98.41	42.41
				Telmisartan	99.15	40.48
11	F11	10±0.00	96 mins	Teneligliptin	97.36	15.88
				Telmisartan	96.25	10.96

Table No.18: Comparative %Drug Release of Bathes (Teneligliptin)

Sr. No.	Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	0	0	0	0	0	0	0.00	0	0	0	0	0
2	60	4.46	2.74	10.16	3.55	3.74	13.48	5.29	11.23	2.28	12.56	2.64
3	120	7.23	5.39	16.21	6.88	7.35	18.02	8.36	16.22	5.27	19.87	3.45
4	180	10.45	8.36	20.23	10.51	10.54	25.20	12.87	20.65	9.34	24.54	5.36
5	240	13.81	11.65	24.41	13.06	12.54	31.69	15.32	25.17	12.36	29.36	8.74
6	300	17.35	14.98	27.87	15.56	15.67	38.56	21.36	29.34	15.23	33.45	11.54
7	360	20.15	17.05	31.56	19.32	19.65	43.76	27.65	33.54	18.65	38.54	13.65
8	420	23.35	19.03	35.61	22.65	23.78	49.45	29.05	38.28	23.48	42.41	15.88

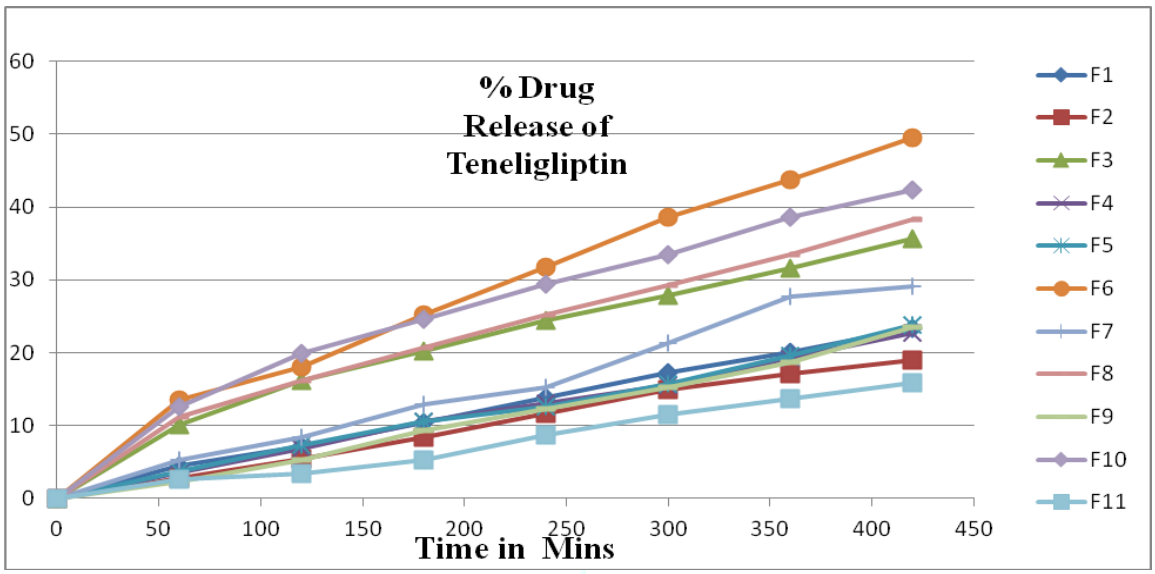

Figure No.11 : Comparative Dissolution Profile of All Batches (Teneligliptin)

Table No.19: Comparative %Drug Release of Bathes (Telmisartan)

Sr. No.	Time (min.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0.00	0	0	0	0	0
1	60	5.23	1.2	5.79	2.87	0.77	7.62	2.63	9.25	3.96	13.48	0.89
3	120	8.66	3.7	9.52	4.98	2.37	11.06	5.98	13.65	5.47	19.56	1.23
4	180	11.56	5.5	13.85	7.22	5.56	16.71	9.23	18.36	8.56	24.32	2.84
5	240	14.25	7.4	17.69	9.36	8.74	23.28	12.34	20.96	11.91	29.89	3.95
6	300	16.32	9.8	21.54	11.87	11.54	29.63	17.36	24.38	14.21	34.13	6.26
7	360	18.58	12.6	24.35	13.21	15.23	37.96	21.03	28.36	16.69	37.33	8.45
8	420	20.53	14.7	27.32	15.32	18.55	43.81	25.3	31.1	19.42	40.48	10.96

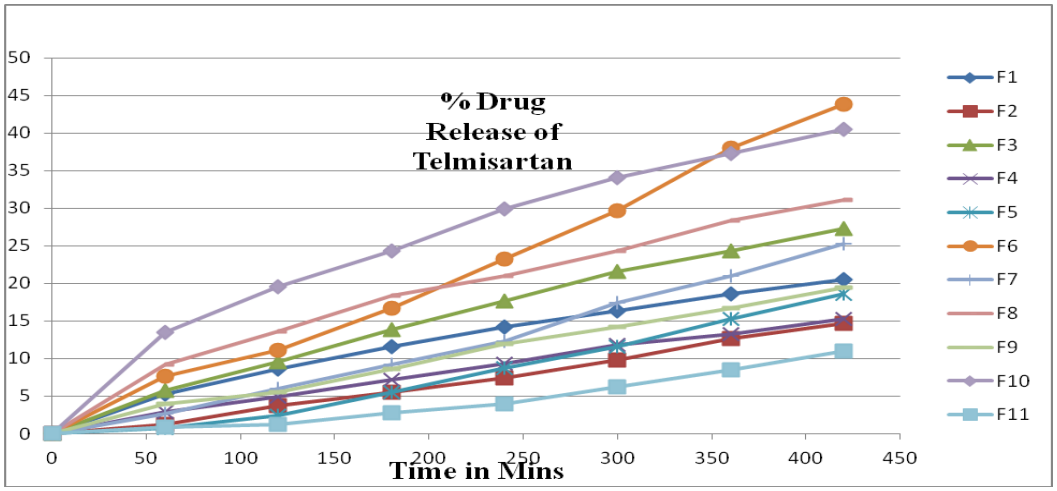

Figure No.12: Comparative Dissolution Profile of All Batches (Telmisartan)

➢ **Stability Study:**

Stability studies of the Best Formulation F6 was carried out by keeping the tablets at room temperature and 40^{0}C ±2^0 C/ 75 ±5 % RH (stability chamber) for 30 days. From the stability studies it was found that formulation were stable at room temperature and 40^{0}C ±2^0 C/ 75 ±5 % RH for a period of 60 days. There was no appreciable and highlighting change in physical properties, drug release and drug content during the testing period. Thus the test indicated stability of formulations.

1. Physical Appearance:

Color: unchanged. **Odour:** unchanged

Table No. 20: Stability Parameters of F6 for 0, 30, 60 Days

Formulations	Study Conditions Specification	Months	Drugs Name	% Drug Content	% Drug Release
F6	40^{0}C ±2^0 C/ 75 ±5 % RH	Initial	Teneligliptin	98.58	49.45
			Telmisartan	98.72	43.81
		30 days	Teneligliptin	98.21	48.64
			Telmisartan	98.44	42..37
		60days	Teneligliptin	97.73	47.58
			Telmisartan	97.84	41.46

➢ **Biological screening**

Animal study:-

Table No.21:- Body weight of albino rats before and after treatment:-

Sr.No	Body wt. before treatment	Body wt. after end of the treatment
Negative Control	241±1.40	229±1.63
Positive Control	240±1.44	242±1.67
Std	220±1.88	210±1.78
4a	260±2.45	255±2.56
4b	250±2.76	262±2.67
4c	250±1.78	270±2.78

Table no. 22:- Blood glucose level

Drug	Blood glucose level mg/dl (Mean ± SEM)				
	0 days	2 days	4 days	6 days	8 days
Negative control	232±2.31	233±2.97	231±1.24	233±2.86	230±2.46
Positive control	115±1.44	116±2.67	118±1.45	114±2.45	115±2.45
Standard	204±2.28	118±2.21	153±1.99	128±2.27	116±1.51
4a	215±4.55	190±4.78	151±1.23	137±1.90	119±3.64
4b	205±3.54	194±2.67	162±2.89	133±1.43	128±3.51
4c	222±1.89	203±1.78	157±2.45	142±1.97	130±1.09

The antidiabetic activity is held and by the observation of blood glucose levels we can say that the Teneligliptin and Telmisartan Combination is useful in the activity.

CONCLUSION:

On the basis of the study, selection of drug candidate and the type of formulation lead to the formulation of Bilayer Tablets to treat Co-existent Type II Diabetes Mellitus and Hypertension were formulated successfully. The addition of magnesium stearate which produce satisfactory results for flow property of powders. Addition of crospovidone improved drug release of Telmisartan layer. The Preformulation study revealed the purity of drug and also it confirmed the stability of drug with excipient hence proved to be compatible there.

All the tablet formulations showed satisfactory results with respect to hardness, friability, disintegration time, drug content and In-vitro dissolution studies. The binder, filler, diluents, lubricants used in the formulations which improve the tablet quality and sustained release agent improve the disintegration and dissolution property of tablets. The powder was granulated by wet granulation and the second layer was compressed above the compressed first layer, it is a good method used for the compression of bilayer tablets. Wet granulation is the best method for formulation of such bilayer tablets. The results obtained in Biological Studies revealed that the present drug combination shows antidiabetic activity. Telmisartan does not hinders the antidiabetic activity of Teneligliptin when taken in combination. Thus, there is no Drug-Drug Interaction between Teneligliptin and Telmisartan. Therefore, this research work concludes the successful was shown the "Formulation and Evaluation of Teneligliptin and Telmisartan Bilayer Tablets for the Treatment of Coexistent Type II Diabetes Mellitus and Hypertension".

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CONFLICT OF INTERESTS

Declared none.

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